Role of hepatic resection in patients with intermediate-stage hepatocellular carcinoma: A multicenter study from Japan

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Transarterial chemoembolization (TACE) is recommended for patients with intermediate-stage (Barcelona Clinic Liver Cancer criteria B [BCLC-B]) hepatocellular carcinoma (HCC). However, patients with BCLC-B HCC can differ in background factors related to hepatic function, as well as tumor size and number. In the present study, we clarified the role of hepatic resection in patients with BCLC-B HCC. A total of 489 BCLC-B HCC patients with Child–Pugh class A disease initially treated with hepatic resection or TACE were included. After propensity score matching (n = 264), hepatic resection (hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.35–0.91) was independently associated with survival in the multivariate analysis. We then divided patients into two groups based on the results of statistical analysis. There were 170 patients treated with resection and 319 with TACE. Child–Pugh score and number of tumors (cut-off, three tumors) were independently associated with type of HCC treatment in the multivariate analysis. We then divided patients in Group A (Child–Pugh score of 5 and ≤3 tumors; n = 186) and Group B (Child–Pugh score of 6 or ≥4 tumors; n = 303). In Group A, cumulative survival was significantly higher in the hepatic resection group than in the TACE group (P = 0.014). In Cox proportional hazards models, hepatic resection (HR, 0.38; 95% CI, 0.23–0.64) was independently associated with survival in Group A patients. In Group B, treatment status was not associated with overall survival. Hepatic resection should be considered in patients with a Child–Pugh score of 5 and ≤3 tumors, despite having BCLC-B HCC.

L iver cancer is the sixth most common cancer and the third most common cause of cancer-related death. It accounts for 7% of all cancers. Hepatocellular carcinoma (HCC), which represents more than 90% of primary liver cancers, is a major health problem globally.[1] Curative treatments such as hepatic resection, liver transplantation, and radiofrequency ablation are indicated in only 30–40% of patients with HCC. Most patients for whom curative treatment is not indicated undergo Transarterial chemoembolization (TACE) or receive sorafenib as palliative therapy.[1]

The BCLC criteria have been used to stage patients with HCC. TACE is recommended for patients with intermediate-stage HCC (BCLC-B).[2–4] However, patients with BCLC-B HCC differ in background factors such as tumor size and number of tumors, which might be why they do not fulfill the Milan criteria.[1,3,5,6] Moreover, liver function in patients with BCLC-B HCC can range from Child–Pugh class A to B. They may have ≥4 tumors irrespective of size, or 2–3 tumors with the largest diameter ≥3 cm in the absence of cancer-related symptoms, macrovascular invasion, or extrahepatic spread.[2]

Japanese clinical guidelines[7,8] recommend several treatments for BCLC-B HCC, including hepatic resection[9] and TACE,[10] depending on the clinical situation. When selecting a therapy, the clinical situation, including liver function and number of tumors, is important.

In the present study, we undertook propensity score matching analysis to clarify the role of hepatic resection in BCLC-B HCC patients with Child–Pugh class A disease. We then determined the clinical factors associated with the type of HCC treatment (i.e., hepatic resection *vs* TACE) in BCLC-B HCC patients with Child–Pugh class A disease. We divided these patients into two groups based on the results of statistical analysis. We clarified the role of hepatic resection in each group.

Materials and Methods

Patients. The study protocol complied with the Declaration of Helsinki and was approved by the institutional review board of each participating institution.

We examined the records of 5020 patients with naïve HCC treated at Ogaki Municipal Hospital (Ogaki), Teine Keijinkai

Hospital (Sapporo), Ehime Prefectural Central Hospital (Matsuyama), Asahi Central Hospital (Asahi), Okayama City Hospital (Okayama), Saiseikai Niigata Daini Hospital (Niigata), or Ehime University Hospital (Matsuyama), Japan, between 2000 and 2015. Of these, 810 patients had BCLC-B HCC. We excluded patients with Child–Pugh class B disease (n = 223) and initial treatment other than hepatic resection or TACE (n = 98). Ultimately, we included 489 patients (hepatic resection group, n = 170; TACE group, n = 319) in this study.

The seven hospitals that participated in the present study are located in different regions of Japan, and each serve as a liver disease center in its region. In addition, each hospital employs specialists in hepatology, surgery, and radiology for HCC to maintain the quality of clinical practice and to prevent treatment-related complications and mortality as much as possible.

The start of the follow-up period was defined at the time when naïve HCC was diagnosed. The end of follow-up was defined as the date of the final visit for patients who remained alive or the date of death for patients who died during the follow-up period.

Diagnosis and treatment of HCC. Hepatocellular carcinoma was diagnosed based on abdominal ultrasonography plus dynamic computed tomography (CT) (hyperattenuation during the arterial phase in part or all of the tumor and hypoattenuation in the portal venous phase), MRI (same as dynamic CT findings), or both, as recommended by the American Association for the Study of Liver Diseases.[11,12] Regarding HCC treatment, the most appropriate treatment method for each patient was selected through discussions between surgeons, hepatologists, and radiologists. After 2005, all treatments were based on the Japanese practice guidelines for HCC,[7,8] when possible. Regarding HCC etiology, patients positive for hepatitis B virus surface antigen were judged to have HCC due to the presence of hepatitis B virus; those positive for anti-hepatitis C virus were judged to have HCC due to the presence of hepatitis C virus.

In the present study, we evaluated liver function using the Child–Pugh score[13] and the ALBI grade,[14] a new liver function grading system. The ALBI score is calculated as [$\log_{10}$ bilirubin (μmol/L) × 0.66] + [albumin (g/L) × −0.085]. Grade 1 corresponds to a score ≤−2.60, grade 2 corresponds to a score from −2.60 to −1.39, and grade 3 corresponds to a score >−1.39.

Surveillance for HCC recurrence after initial treatment. Follow-up consisted of regular blood tests and tumor marker AFP monitoring every 3 months. Dynamic CT, MRI, or both were carried out every 3–4 months after initial treatment for HCC. When HCC recurrence or disease progression was detected based on radiologic findings, the most appropriate therapy was initiated in each patient.

Statistical analysis. Continuous variables are expressed as medians (interquartile range). The Mann–Whitney U-test was used for continuous variables. The χ^2-test with Fisher's exact test was used for categorical variables.

To reduce the confounding effects of covariates, we used propensity scores to match patients who underwent hepatic resection to unique patients who received TACE. The following five covariates related to prognosis of HCC at the start of follow-up were taken into account: age, sex, ALBI grade, and number of tumors. We first calculated the propensity scores using these five covariates. These scores were then rounded to two decimal places. We conducted one-to-one patient matching based on these propensity scores. Discrimination in the propensity score model was assessed using area under the ROC curve,[15] with higher values indicating better discrimination. Calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test.[16] The Hosmer–Lemeshow test compares model performance (observed *vs* expected) across deciles of risk to test whether the model is biased (i.e., performs differently at the extremes of risk). A non-significant value for the Hosmer–Lemeshow test suggests the absence of such bias.

Multivariate logistic regression with backward elimination was used to select covariates related to type of HCC treatment (i.e., hepatic resection *vs* TACE).

Receiver–operating characteristic analysis was used for determining the cut-off values for covariates that were identified using multivariate logistic regression analysis. The cut-off values were calculated using the Youden index (maximum [sensitivity + specificity −1]).[17]

Actuarial analysis of cumulative survival was carried out using the Kaplan–Meier method, and differences were tested using the log–rank test. Cox proportional hazards models with backward elimination were used to calculate HRs for overall survival.

In the multivariate analysis, we used the covariates that were associated with HCC treatment type, risk factors for HCC, and prognostic factors related to liver fibrosis and function in patients with chronic liver disease.[1,18,19]

Propensity score analysis was undertaken with SPSS version 21.0 for Windows (IBM Japan, Tokyo, Japan). Other statistical analyses were carried out with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[20] More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics. Table 1 shows the characteristics of the study patients at the start of follow-up. There were 81 women and 408 men with a median age of 71 years (range, 64–76 years). Median follow-up was 2.2 years (range, 1.1–

Table 1. Characteristics of study patients with intermediate-stage hepatocellular carcinoma (HCC) (n = 489)

Age, years†	71.0 (64.0–76.0)
Sex, female/male	81/408
Etiology, hepatitis B/C/B+C/non-B, non-C	66/298/5/120
AST, IU/L	58 (39–85)
ALT, IU/L	54 (33–80)
Albumin, g/dL†	3.8 (3.6–4.1)
Total bilirubin, mg/dL†	0.8 (0.6–1.0)
Platelet count, ×10³/m³†	13.8 (9.6–17.7)
Prothrombin time, %†	89.0 (81.0–98.0)
AFP, ng/mL†	33.1 (10.4–295.9)
Child–Pugh score, 5/6	337/152
ALBI grade, 1/2	208/281
Maximum tumor size, cm†	4.3 (3.2–6.0)
Number of tumors†	3 (2–5)
HCC treatment type, resection/TACE	170/319
Follow-up duration, years†	2.2 (1.1–4.2)

†Data expressed as medians (interquartile range). AFP, α-fetoprotein; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TACE, transcatheter arterial chemoembolization.
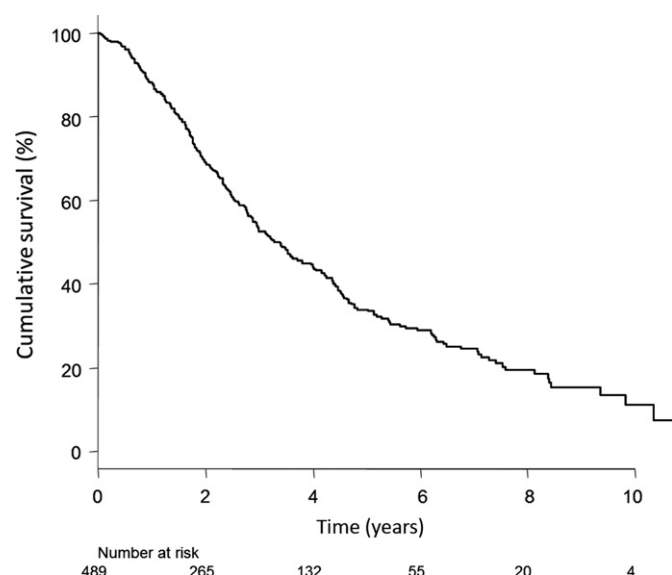
Fig. 1. Cumulative survival curve for all study patients with intermediate-stage hepatocellular carcinoma (n = 489).

Table 2. Characteristics of study patients with intermediate-stage hepatocellular carcinoma (HCC) after propensity score matching (n = 264)

	Resection group (n = 132)	TACE group (n = 132)	P-value
Age, years†	69 (63–75)	69 (63–75)	0.696
Sex, female/male	22/110	23/109	1.000
Etiology, hepatitis B/C/B+C/non-B, non-C	25/76/0/31	16/82/3/31	0.171
AST, IU/L	50 (36–80)	59 (43–92)	0.082
ALT, IU/L	51 (32–77)	56 (33–77)	0.962
Albumin, g/dL†	3.9 (3.7–4.2)	3.9 (3.6–4.1)	0.419
Total bilirubin, mg/dL†	0.7 (0.6–0.9)	0.8 (0.6–1.0)	0.140
Platelet count, ×10³/m³†	14.8 (10.9–17.4)	14.0 (9.5–18.2)	0.252
Prothrombin time, %†	90 (85–99)	89 (80–100)	0.329
AFP, ng/mL†	14.5 (5.9–61.0)	14.1 (6.3–43.6)	0.916
Child–Pugh score, 5/6	103/29	89/43	0.072
ALBI grade, 1/2	66/66	66/66	1.000
Maximum tumor size, cm†	4.6 (3.6–6.2)	4.0 (3.2–5.7)	0.012
Number of tumors†	2 (2–4)	3 (2–4)	0.056
Follow-up duration, years†	2.5 (1.4–4.9)	2.3 (1.2–4.3)	0.486

†Data expressed as medians (interquartile range). Group A, Child–Pugh score of 5 and ≤3 tumors. AFP, α-fetoprotein; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization.

4.2 years). There were 337 patients with a Child–Pugh score of 5 and 152 patients with a score of 6. The median size of the largest tumor was 4.3 (3.2–6.0) cm and the median number of tumors was 3 (2–5).

The 3-, 5-, and 7-year cumulative survival rates were 52.5%, 33.9%, and 24.5%, respectively (Fig. 1). Median survival was 3.4 (95% CI, 2.9–4.0) years.

Propensity score matching analysis. The P-value of the calculated propensity scores based on the Hosmer–Lemeshow test was 0.356.[16] The area under the curve of the ROC–calculated propensity score was 0.78 (95% CI, 0.73–0.82).[15] The baseline characteristics of the 264 study patients after propensity score matching are summarized in Table 2. There were no significant differences between the hepatic resection and TACE groups other than maximum tumor size. The 3-, 5-, and 7-year cumulative survival rates in patients who underwent hepatic resection were 63.4%, 53.1%, and 38.0%, respectively, and 53.0%, 34.1%, and 24.8% in patients who received TACE, respectively (P = 0.020) (Fig. 2). Median survival in the hepatic resection patients was 5.4 (95% CI, 3.2–6.8) years and 3.5 (95% CI, 2.4–4.2) years in the TACE patients. Cox proportional hazards models that included the covariates of age, sex, etiology, platelet count, ALBI grade, AFP level, number of tumors, tumor diameter, and type of HCC treatment showed that age ≥75 years (HR, 2.23; 95% CI, 1.33–3.74; P = 0.002) and hepatic resection (HR, 0.56; 95% CI, 0.35–0.91; P = 0.012) were independently associated with survival (Table 3).

Multivariate analysis for HCC treatment type and ROC curve analysis. Multivariate logistic regression that included the covariates related to etiology, total bilirubin level, platelet count, AFP level, Child–Pugh score, and number of tumors showed that a Child–Pugh score of 6 (odds ratio, 0.43; 95% CI, 0.25–0.73; P = 0.020) and number of tumors (per tumor) (odds ratio, 0.60; 95% CI, 0.51–0.69; P < 0.001) were independently associated with the selection of hepatic resection as the treatment for HCC. The ROC analysis showed that the cutoff values for the number of tumors were 3 (Fig. 3).

Group classification based on multivariate logistic regression analysis. Based on the multivariate logistic regression analysis,
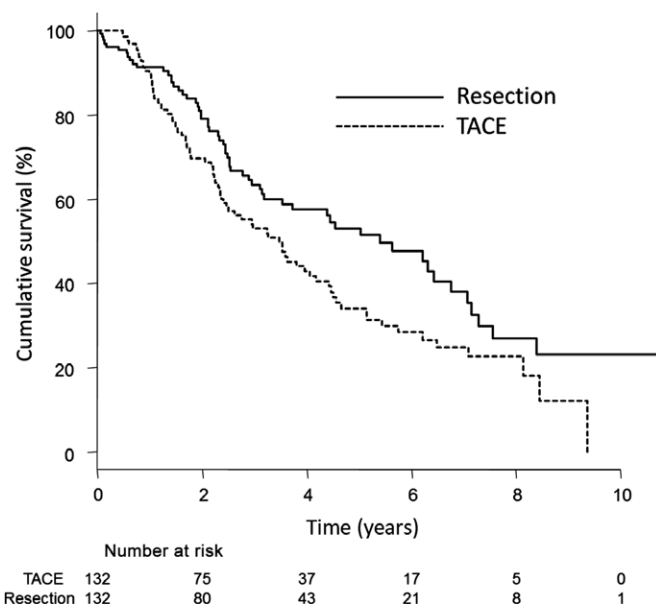

Fig. 2. Cumulative survival curve for patients with intermediate-stage hepatocellular carcinoma after propensity score matching. The hepatic resection and transarterial chemoembolization (TACE) groups had significantly different cumulative survival rates (P = 0.020).
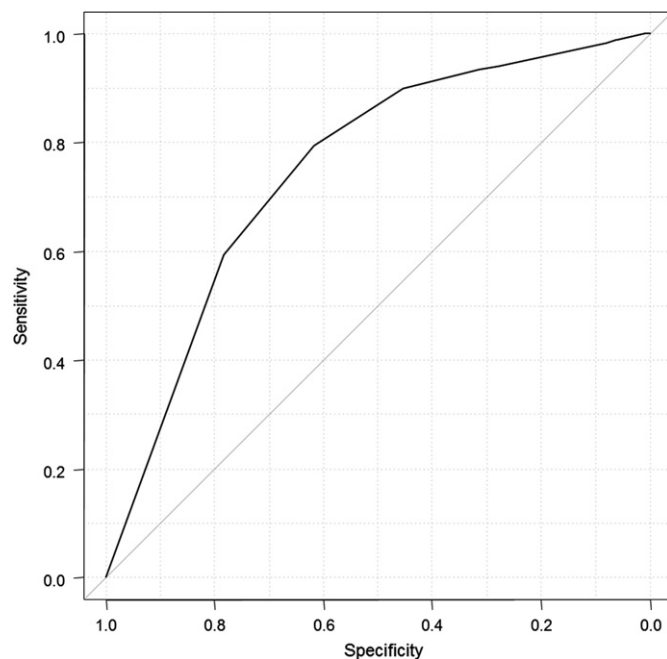
we divided the study patients into Group A (Child–Pugh score of 5 and ≤3 tumors; n = 186) and Group B (Child–Pugh score of 6 or ≥4 tumors; n = 303). We then undertook survival analysis comparing patients who underwent hepatic resection and TACE in each group.

Characteristics and survival analysis for Group A. Table 4 shows the characteristics of Group A patients at the start of

Table 3. Multivariate analysis of factors related to survival in patients with intermediate-stage hepatocellular carcinoma after propensity score matching

Factor	Hazard ratio	95% CI	P-value
Age			
<75 years (*n* = 190)	1.00	1.33–3.74	0.002
≥75 years (*n* = 74)	2.23		
Treatment			
TACE (*n* = 132)	1.00	0.35–0.91	0.012
Resection (*n* = 132)	0.56		

CI, confidence interval; TACE, transcatheter arterial chemoembolization.

Fig. 3. Receiver–operating characteristic curve for the number of tumors and type of treatment for hepatocellular carcinoma.

Table 4. Characteristics of patients with intermediate-stage hepatocellular carcinoma, Child–Pugh score of 5, and three or more tumors (Group A) (*n* = 186)

	Resection group (*n* = 110)	TACE group (*n* = 76)	P-value
Age, years†	71 (64–74)	73 (66–76)	0.114
Sex, female/male	18/92	9/67	0.526
Etiology, hepatitis B/C/B+C/non-B, non-C	24/49/0/37	6/48/2/20	0.005
AST, IU/L	48 (35–71)	57 (41–67)	0.363
ALT, IU/L	49 (32–73)	51 (31–70)	0.962
Albumin, g/dL†	4.1 (3.8–4.3)	3.9 (3.7–4.1)	0.002
Total bilirubin, mg/dL†	0.7 (0.6–0.9)	0.8 (0.6–0.9)	0.316
Platelet count, ×10^3/m³†	14.8 (10.6–17.4)	14.7 (10.1–18.7)	0.948
Prothrombin time, %†	91 (86–100)	93 (87–102)	0.483
AFP, ng/mL†	14.7 (4.4–109.6)	20.9 (5.9–586.2)	0.349
ALBI grade, 1/2	75/35	37/39	0.001
Maximum tumor size, cm†	4.8 (3.8–6.2)	4.5 (3.5–6.2)	0.522
Number of tumors†	2 (2–2)	2 (2–3)	<0.001
Follow-up duration, years†	3.1 (2.0–5.2)	2.4 (1.2–4.4)	0.051

†Data expressed as medians (interquartile range). AFP, α-fetoprotein; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization.

hepatic resection were 50.4%, 47.4%, and 25.3%, respectively, and 45.1%, 22.5%, and 16.3%, respectively, in patients who received TACE (*P* = 0.088) (Fig. 4b). Median survival in the hepatic resection patients was 3.2 (95% CI, 2.3–6.4) years and 2.8 (95% CI, 2.2–3.4) years in the TACE patients.

Cox proportional hazards models that included the covariates of age, sex, etiology, platelet count, ALBI grade, AFP level, number of tumors, tumor diameter, and type of HCC treatment showed that age ≥75 years (HR, 2.02; 95% CI, 1.38–2.97; *P* < 0.001), platelet count ≥13.0 × 10^3/m³ (HR, 0.68; 95% CI, 0.47–0.98; *P* = 0.038), AFP level ≥100 ng/mL (HR, 1.83; 95% CI, 1.27–2.64; *P* = 0.001), ≥4 tumors (HR, 1.65; 95% CI, 1.15–2.34; *P* = 0.006), and tumor size ≥5 cm (HR, 1.69; 95% CI, 1.17–2.44; *P* = 0.005) were independently associated with survival in Group B (Table 7).

Discussion

In the present multicenter study that included a large number of BCLC-B HCC patients with Child–Pugh class A disease, the multivariate Cox proportional hazards models that included age, sex, etiology, platelet count, ALBI grade, AFP level, number of tumors, tumor diameter, and type of HCC treatment as covariates showed that hepatic resection was independently associated with survival in patients after propensity score matching (HR, 0.56). In addition, multivariate logistic regression that included etiology, total bilirubin level, platelet count, AFP level, Child–Pugh score, and number of tumors as covariates showed that Child–Pugh score and number of tumors are independently associated with type of HCC treatment (i.e., hepatic resection *vs* TACE). Based on the Youden index in the ROC analysis, the cut-off value for the number of tumors was 3. The Kaplan–Meier method with log–rank test showed that study patients with a Child–Pugh score of 5 and ≤3 tumors in

follow-up. Patients who underwent hepatic resection (*n* = 110) or TACE (*n* = 76) differed in etiology, albumin level, ALBI grade, and number of tumors. The 3-, 5-, and 7-year cumulative survival rates in patients who underwent hepatic resection were 67.1%, 54.2%, and 41.5%, respectively, and 55.0%, 32.0%, and 22.9% in patients who received TACE, respectively (*P* = 0.014) (Fig. 4a). Median survival in the hepatic resection patients was 5.4 (95% CI, 3.7–7.1) years and 3.5 (95% CI, 2.4–4.5) years in TACE patients.

Cox proportional hazards models that included the covariates of age, sex, etiology, platelet count, ALBI grade, AFP level, number of tumors, and type of HCC treatment showed that hepatic resection (HR, 0.38; 95% CI, 0.23–0.64; *P* < 0.001) and 3 tumors (HR, 2.05; 95% CI, 1.20–3.49; *P* = 0.008) were independently associated with survival in Group A (Table 5).

Characteristics and survival analysis for Group B. Table 6 shows the characteristics of Group B patients at the start of follow-up. Patients who underwent hepatic resection (*n* = 60) or TACE (*n* = 243) differed in age, platelet count, ALBI grade, number of tumors, and tumor diameter. The 3-, 5-, and 7-year cumulative survival rates in patients who underwent
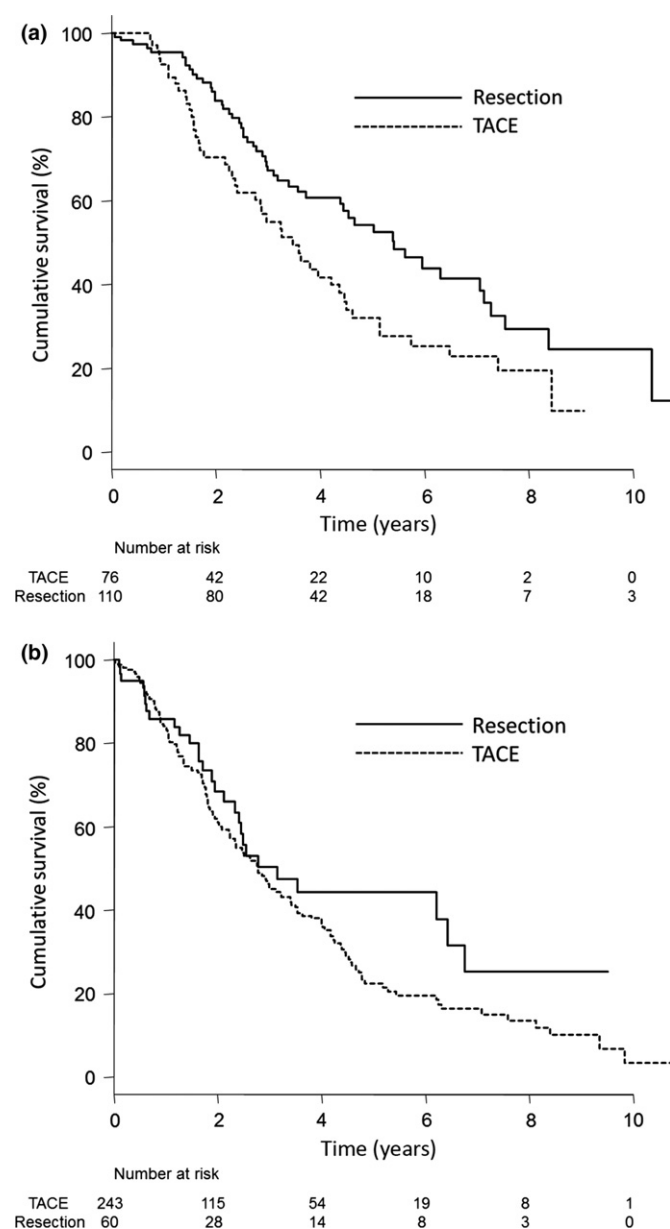
Fig. 4. (a) Cumulative survival curve for patients with intermediate-stage hepatocellular carcinoma (HCC), Child–Pugh score of 5, and ≤3 tumors (Group A) (n = 186). The hepatic resection and transarterial chemoembolization (TACE) groups had significantly different cumulative survival rates (P = 0.014). (b) Cumulative survival curve for patients with intermediate-stage HCC, Child–Pugh score of 6, or ≥4 tumors (Group B) (n = 303). There was no significant difference in cumulative survival rates between patients who underwent hepatic resection and those who underwent TACE (P = 0.088).

Table 5. Multivariate analysis of factors related to survival in patients with intermediate-stage hepatocellular carcinoma, Child–Pugh score of 5, and three or more tumors (Group A)

Factor	Hazard ratio	95% CI	P-value
Treatment			
TACE (n = 76)	1.00	0.23–0.64	<0.001
Resection (n = 110)	0.38		
Number of tumors			
2 (n = 124)	1.00	1.20–3.49	0.008
3 (n = 62)	2.05		

CI, confidence interval; TACE, transcatheter arterial chemoembolization.

Table 6. Characteristics of patients with intermediate-stage hepatocellular carcinoma, Child–Pugh score of 6, and four or more tumors (Group B) (n = 303)

	Resection group (n = 60)	TACE group (n = 243)	P-value
Age, years†	67 (62–76)	72 (65–76)	0.024
Sex, female/male	9/51	45/198	0.578
Etiology, hepatitis B/C/B+C/non-B, non-C	10/40/0/10	26/161/3/53	0.466
AST, IU/L	54 (35–85)	63 (44–94)	0.077
ALT, IU/L	53 (35–84)	58 (34–85)	0.359
Albumin, g/dL†	3.9 (3.5–4.1)	3.7 (3.5–4.0)	0.280
Total bilirubin, mg/dL†	0.7 (0.6–0.9)	0.8 (0.6–1.0)	0.130
Platelet count, $\times 10^3/m^3$ †	14.9 (11.1–19.0)	12.3 (8.9–17.2)	0.021
Prothrombin time, %†	89 (81–97)	86 (79–96)	0.181
AFP, ng/mL†	36.8 (11.3–702.9)	43.0 (13.7–288.0)	0.998
Child–Pugh score, 5/6	27/33	124/119	0.471
ALBI grade, 1/2	26/34	70/173	0.043
Maximum tumor size, cm†	4.5 (3.4–6.3)	3.8 (2.7–5.6)	0.009
Number of tumors†	4 (2–5)	5 (4–7)	<0.001
Follow-up duration, years†	1.9 (1.1–3.3)	1.9 (0.9–3.5)	0.917

†Data expressed as medians (interquartile range). AFP, α-fetoprotein; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization.

the hepatic resection group had higher cumulative survival than their counterparts in the TACE group (P = 0.014). Furthermore, in the multivariate Cox proportional hazards models, hepatic resection was independently associated with survival in this patient group (HR, 0.33). Conversely, study patients with a Child–Pugh score of 6 or ≥4 tumors in the hepatic resection and TACE groups did not differ in cumulative survival. For this patient group, HCC treatment type was not associated with survival in our multivariate Cox proportional hazards models.

Recently, Wada et al.[21] studied the selection criteria for hepatic resection in 85 patients with BCLC-B HCC who underwent hepatic resection (approximately 90% [75/85] of patients in their study had Child–Pugh class A disease). They divided patients into three types based on the number of tumors and maximum tumor diameter on radiologic studies: type 1, up to 3 lesions <5 cm; type 2, up to 3 lesions ≥5 cm or 4 tumors of any size; and type 3, >4 tumors. They found that type 1 patients had better overall survival than type 3 patients. The prognosis of type 2 patients was worse than that of type 1 patients and better than that of type 3 patients. They concluded that their subclassification system is useful for making decisions regarding hepatic resection for BCLC-B HCC patients with multiple tumors. However, all of the patients in the present study had good liver function (Child–Pugh class A disease). Our study included a large number of patients and the subclassification of BCLC-B HCC was simpler than the

Table 7. Multivariate analysis of factors related to survival in patients with intermediate-stage hepatocellular carcinoma, Child–Pugh score of 6, and four or more tumors (Group B) (*n* = 303)

Factor	Hazard ratio	95% CI	*P*-value
Age			
<75 years (*n* = 168)	1.00	1.38–2.97	<0.001
≥75 years (*n* = 75)	2.02		
Platelet count			
<13.0 × 10³/m³ (*n* = 117)	1.00	0.47–0.98	0.038
≥13.0 × 10³/m³ (*n* = 100)	0.68		
AFP			
<100 ng/mL (*n* = 120)	1.00	1.27–2.64	0.001
≥100 ng/mL (*n* = 69)	1.83		
Number of tumors			
<4 (*n* = 98)	1.00	1.15–2.34	0.006
≥4 (*n* = 145)	1.65		
Maximum tumor size			
<5 cm (*n* = 163)	1.00	1.17–2.44	0.005
≥5 cm (*n* = 80)	1.69		

AFP, α-fetoprotein; CI, confidence interval.

system proposed by Wada and colleagues. We stratified patients based on clinical factors that were identified in the multivariate analysis as associated with type of HCC treatment. In addition, the cut-off values for continuous clinical factors used for subclassification were determined using statistical analysis. We compared overall survival in patients who underwent hepatic resection versus TACE. In general, TACE is recommended for patients with BCLC-B HCC.[2–4] Therefore, patients who underwent TACE were considered necessary as the referent group to demonstrate the utility of resection in patients with BCLC-B HCC.

In the present study, we used the covariates of age, sex, etiology, platelet count, ALBI grade, and AFP level in our multivariate Cox proportional hazards models. These clinical factors were previously reported as risk factors for HCC or associated with liver fibrosis and liver function in patients with chronic liver disease.[1,18,19] In addition, we recently reported the utility of the ALBI grade, a simple method for evaluating liver function using only albumin and total bilirubin levels.[14,22,23] In Group A, these clinical risk factors were not statistically significantly associated with overall survival. Therefore, we believe that hepatic resection should be considered as a radical treatment option for patients with a Child–Pugh score of 5 and 2 tumors irrespective of size, even though they have BCLC-B HCC. Conversely, in Group B, several clinical factors other than type of HCC treatment were found to be associated with overall survival in the multivariate analysis. In the present study, we did not include tumor size in the multivariate logistic regression analysis for type of HCC treatment. There is a range of tumor sizes among patients with BCLC-B HCC. Actually, in Group A, patients who underwent hepatic resection and TACE had tumors of similar size.

Japanese clinical practice guidelines for HCC[7,8] recommended hepatic resection for 2–3 tumors with Child–Pugh A or B. The advantage of our study was to clarify that hepatic resection is more recommended in the patients with a Child–Pugh score of 5 and 2 tumors among the patients with Child–Pugh class A and 2–3 tumors.

The main limitations of this study include its hospital-based population and retrospective nature. In addition, the median follow-up period was relatively short. Although the present study included a large number of patients from multiple centers in Japan, further prospective studies with community-based subjects and long term follow-up are warranted. Another limitation of this study was that it only focused on BCLC-B HCC patients with Child–Pugh class A disease. Further studies of BCLC-B HCC patients with both Child–Pugh class A and B disease are warranted. Additionally, we did not investigate the recurrence-free survival and the recurrence type of HCC in the present study. Further studies considering recurrence information for HCC are warranted.

In conclusion, hepatic resection should be considered as a radical treatment for patients with a Child–Pugh score of 5 and ≤3 tumors (especially 2 tumors), even though their HCC is staged as BCLC-B. Further studies are warranted to confirm these findings in other patient groups.

Disclosure Statement

The authors have no conflicts of interest.

Abbreviations

AFP	α-fetoprotein
ALBI	albumin-bilirubin
BCLC	Barcelona Clinic Liver Cancer
BCLC-B	Barcelona Clinic Liver Cancer criteria B
CI	confidence interval
CT	computed tomography
HCC	hepatocellular carcinoma
HR	hazard ratio
ROC	receiver–operating characteristic
TACE	transarterial chemoembolization

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